40 CFR Parts 795 and 799

[OPTS-42084F; FRL 3473-3]

Commercial Hexane; Proposed Pharmacokinetics Test Requirements and Revision of Proposed Test Guideline

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule.

SUMMARY: EPA is reproposing under section 4(a) of the Toxic Substances Control Act (TSCA) the pharmacokinetics test requirements and the associated test guideline for commercial hexane. This proposed rule complements a final test rule (53 FR 3382; February 5, 1988) issued under section 4(a)(1)(B) of TSCA that requires manufacturers and processors of commercial hexane to test it for subchronic toxicity, oncogenicity, reproductive toxicity, developmental toxicity, mutagenicity, neurotoxicity, and pharmacokinetics.

DATES: Submit written comments on or before December 27, 1988. If persons request an opportunity to submit oral comments by December 9, 1988, EPA will hold a public meeting on this proposed rule in Washington, DC. For further information on arranging to speak at this meeting, see Unit VII of this preamble. The incorporation by reference in this rule shall become effective 44 days after date of publication of the final rule in the Federal Register.

ADDRESS: Submit written comments, identified by the document control number (OPTS-42084F) in triplicate to: TSCA Public Docket Office (TS-793), Office of Toxic Substances, Environmental Protection Agency, Room NE-G004, 401 M Street SW., Washington, DC 20460.

FOR FURTHER INFORMATION CONTACT: Michael M. Stahl, Acting Director, TSCA Assistance Office (TS-799), Office of Toxic Substances, Room EB-44, 401 M Street SW., Washington, DC 20460, (202) 554-1404, TDD (202) 554-0551.

SUPPLEMENTARY INFORMATION: EPA is reproposing the pharmacokinetics test requirements and the associated test guideline in 40 CFR 795.323 for commercial hexane (previously proposed May 15, 1986, 51 FR 17854).

Public reporting burden for this collection of information is estimated to average 535 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M Street, SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503

I. Background

On May 15, 1986, EPA proposed pharmacokinetics testing of commercial hexane at 40 CFR 795.232 (51 FR 17854). Prior to issuing the final test rule for commercial hexane (53 FR 3382; February 5, 1988), EPA determined from an internal review that inadequacies in the proposed guideline for pharmacokinetics testing would limit the ability to obtain meaningful data. When the final test rule for commercial hexane was issued, EPA required that test sponsors perform pharmacokinetics testing but stated that it would propose a revised test standard and reporting requirements at a later date. EPA is now proposing a revised test standard and reporting requirements.

II. Proposed Pharmacokinetics Test Standard

EPA is proposing that the required pharmacokinetics testing for commercial hexane be conducted according to the inhalation and dermal pharamcokinetics test guideline described in this rule. Pharmacokinetics testing is necessary to determine the absorption, distribution metabolism, and excretion of commercial hexane by inhalation and dermal routes of administration. Data from these studies will help EPA evaluate whether exposure to commercial hexane presents an unreasonable risk of injury to human health.

The purposes of these studies are to: (1) Compare the pahrmacokinetics and metabolism of commercial hexane after inhalation and dermal administration. (2) compare the bioavailability of commercial hexane after inhalation and dermal administration and (3) examine the effects of repeated doses on the pharmacokinetics and metabolism of commercial hexane.

EPA proposes that investigators use 7- to 9-week old rats and 5- to 7-week old female guinea pigs for these studies. Both species have been used extensively for percutaneous absorption studies. Two doses would be required in these studies, a "low" dose and a "high" dose. The "high" dose should ideally induce some measurable toxicity such as weight loss. The "low" dose should correspond to a no observed effect level (NOEL). If possible, the same "high" and "low" doses would be administered by inhalation and dermal contact. The proposed studies would measure blood concentrations, urinary and fecal excretion, and metabolites of the test substances.

As stated in the February 5, 1988 preamble, EPA agrees with the American Petroleum Institute (API) that isotopically labelling all component of commercial hexane would be excessively burdensome. Consequently, EPA is proposing that each pharmacokinetics test described in this document be performed separately with commercial hexane containing two different radiolabeled test substances.

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As suggested by API, one test mixture would contain ^{14}C methycyclopentane (MCP) and the other would contain ^{14}C *n*-hexane. (Ref. 1). An intravenous test has also been added to the protocol to obtain baseline information on the metabolism and excretion of the test substances when it is completely absorbed. This data would permit comparisons of absorption and metabolic processes operating via dermal and inhalation routes of exposure by monitoring excretion (urine, feces, expired air) of test substances during the study and tissue distribution of test substances at the end of the study.

EPA believes that this test methodology will provide the basis for a valid and scientifically acceptable test. EPA is proposing that the test guideline described in this document be adopted as the test standard for the pahrmacokinetics studies on commercial hexane. All persons conducting tests would submit plans and conduct tests in compliance with the TSCA Good Labaratory Practice (GLP) Standards found in 40 CFR Part 792.

III. Reporting Requirements

All data developed under this proposed rule would be reported in accordance with TSCA GLPL Standards.

As described in 40 CFR 790.50 under single-phase rulemaking procedures, test sponsors would submit a study plan no later than 45 days before the initiation of pharmacokinetics testing.

EPA is required by TSCA section 4(b)(1)(C) to specify the time period during which persons subject to a test rule must submit test data. EPA is proposing that the test sponsors complete the pharmacokinetics testing and submit the final report to EPA within 18 months of the effective date of the final test rule establishing pharmacokinetics tests standards and reporting requirements. Interim progress reports would be provided to EPA at 6-month intervals, beginning 6 months after the effective date of the final rule establishing test standards and reporting requirements for the required pharmacokinetics testing, until the final report has been submitted to EPA.

IV. Issues for Comment

EPA is soliciting comments on the suitability of the revised inhalation and dermal pharmacokinetics test standard proposed by the Agency for the testing of commercial hexane.

V. Economic Analysis

To assess the potential economic impact of the final test rule for commercial hexane published in the **Federal Register** of February 5, 1988, EPA has estimated the cost of the testing regimen. Total test costs for the final test rule were estimated to range from $2.2 to $2.9 million. As a result of these costs, EPA determined that the likelihood of significant adverse economic impact was low for the manufacturers of commercial hexane.

In accordance with the specifics of this new protocol, EPA has reevaluated the cost of conducting pharmacokinetics testing on commercial hexane. This procedure is estimated at $208,000 to $262,000. This revised estimate is discussed in more detail in a memorandum in the rulemaking record (Ref. 2).

On the basis of the costs estimated in the economic analysis for the final commercial hexane test rule, and the incremental cost of this pharmacokinetics procedure, the additional testing cost will not result in any change from the conclusions of the prior economic analysis. Refer to the economic impact analysis of the final test rule for commercial hexane for a complete discussion of potential economic impact.

VI. Availability of Test Facilities and Personnel

Section 4(b)(1) of TSCA requires EPA to consider "* * * the reasonably foreseeable availability of the facilities and personnel needed to perform the testing required under the rule." Therefore, EPA conducted a study to assess the availability of test facilities and personnel to handle the additional demand for testing services created by section 4 test rules. Copies of the study, Chemical Testing Industry: Profile of Toxicological Testing, can be obtained through the National Technical Information Service (NTIS), 5285 Port Royal Road, Springfield, VA 22161 (PB 82-140773). On the basis of this study, EPA believes that there will be test facilities and personnel available to perform the testing proposed in this rule.

VII. Public Meetings

If persons indicate to EPA that they wish to present oral comments on this proposed rule to EPA officials who are directly responsible for developing the rule and supporting analyses, EPA will hold a public meeting in Washington, DC subsequent to the close of the public comment period. Persons who wish to attend or to present comments at the meeting should call the TSCA Assistance Office (TAO): (202) 554-1404, by December 9, 1988. A meeting will not be held if members of the public do not indicate that they wish to make oral presentations. While the meeting will be open to public, active participation will be limited to those persons who arrange to present comments and to designated EPA participants. Persons wishing to attend should call the TAO before making travel plans to verify whether a meeting will be held.

Should a meeting be held, EPA would transcribe the meeting and include the written transcript in the rulemaking record. Participants are invited, but not required, to submit copies of their statements prior to or on the day of the meeting. All such written materials will become part of EPA's record for this rulemaking.

VIII. Rulemaking Record

EPA has established a record for this rulemaking (docket number OPTS-42084F). This record includes the basic information considered by EPA in developing this rule and appropriate **Federal Register** notices.

This record includes the following information:

A. Supporting Documentation

(1) **Federal Register** notices pertaining to this proposed test standard consisting of:

(a) Notice of final rule of EPA's TSCA Good Laboratory Practice Standards (48 FR 53922; November 29, 1983).

(b) Notice of proposed test rule on methylcyclopentane and commercial hexane (51 FR 17854; May 15, 1986).

(c) Notice of final test rule for commercial hexane and methylcyclopentane (53 FR 3382; February 5, 1988).

B. References

(1) American Petroleum Institute (API). Letter from Steven M. Swanson, Director, Health and Environmental Affairs Department, to USEPA, transmitting comments on the MCP and commercial hexane proposed test rule (September 15, 1986).

(2) USEPA. Internal memorandum from Mark Dreyfus, Regulatory Impacts Branch, to Catherine Roman, Test Rules Development Branch, discussing the cost of the new pharmacokinetics testing protocol for commercial hexane (August 2, 1988).

Confidential Business Information (CBI), while part of the record, is not available for public review. A public version of the record, from which CBI has been deleted, is available for inspection in the TSCA Public Docket Office, NE-GOO4, 401 M St. SW., Washington, DC, from 8 a.m. to 4 p.m., Monday through Friday, except legal holidays.

IX. Other Regulatory Requirements

A. Executive Order 12291

EPA has judged that the final test rule for commercial hexane was not subject to the requirement of a Regulatory Impact Analysis under Executive Order 12291. EPA has determined that this proposed test rule for pharmacokinetics testing does not alter this determination.

This proposed rule was submitted to the Office of Management and Budget (OMB) for review as required by Executive Order 12291. Any written comments from OMB to EPA, and any EPA response to those comments, are included in the rulemaking record.

B. Regulatory Flexibility Act

Under the Regulatory Flexibility Act, (5 U.S.C. 601 *et seq.*, Pub. L. 96-354, September 19, 1980), EPA has certified that the final test rule for commercial hexane would not have a significant impact on a substantial number of small businesses. The proposed pharmacokinetics test standard and reporting requirements do not change this determination.

C. Paperwork Reduction Act

OMB has approved the information collection requirements contained in this proposed rule under the provisions of the Paperwork Reduction Act, 44 U.S.C. 3501 *et seq.* and has assigned OMB control number 2070-0033.

Public reporting burden for this collection of information is estimated to average 535 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Chief, Information Policy Branch, PM-223, U.S. Environmental Protection Agency, 401 M St. SW., Washington, DC 20460; and to the Office of Information and Regulatory Affairs, Office of Management and Budget, Washington, DC 20503, marked "Attention: Desk Officer for EPA." The final rule will respond to any OMB or public comments on the information collection requirements contained in this proposal.

List of Subjects in 40 CFR Parts 795 and 799

Chemicals, Environmental protection, Hazardous substances, Laboratories, Recordkeeping and reporting requirements, Testing.

Dated: November 1, 1988.

Susan F. Vogt,

Acting Assistant Administrator for Pesticides and Toxic Substances.

Therefore, it is proposed that 40 CFR Chapter I, Subchapter R, be amended as follows:

1. In Part 795:

PART 795—[AMENDED]

a. The authority citation would continue to read as follows:

Authority: 15 U.S.C. 2603.

b. By adding new § 795.232 to read as follows:

§ 795.232 Inhalation and dermal pharmacokinetics of commercial hexane.

(a) *Purposes.* The purposes of these studies are to:

(1) Determine the bioavailability of the test substances after dermal and inhalation administration.

(2) Compare the pharmacokinetics and metabolism of the test substances after intravenous, dermal, and inhalation administration.

(3) Examine the effects of repeated doses on the pharmacokinetics and metabolism of the test substances.

(b) *Definitions.* (1) "Bioavailability" refers to the rate and relative amount of administered test substance which reaches the systemic circulation.

(2) "Metabolism" means the study of the processes by which a particular substance is absorbed, distributed, biotransformed, stored, and excreted by the body.

(3) "Percent absorption" means 100 times the ratio of the total radioactivity excreted following dermal or inhalation administration and total radioactivity excreted following intravenous administration of the test substance.

(4) "Pharmacokinetics" means the study of the rates of absorption, tissue distribution, biotransformation, and excretion.

(5) "Low dose" should correspond to the no-observed-effect level (NOEL).

(6) "High dose" should induce some measurable effect such as weight loss.

(7) "Test substance" refers to the nonradioactive and both radiolabeled mixtures (^{14}C *n*-hexane and ^{14}C methylcyclopentane) of commercial hexane used in the testing.

(c) *Test procedures*—(1) *Animal selection*—(i) *Species.* The rat shall be used for pharmacokinetics testing because it has been used extensively for metabolic and toxicological studies. The female guinea pig shall be used for dermal bioavailability tests.

(ii) *Animal strains.* Adult male and female rats and female guinea pigs shall be used for testing. The rats shall be 7 to 9 weeks old and their weight range should be comparable from group to group. The female guinea pigs shall be 5 to 7 weeks old, and their weight range should be comparable from group to group. The animals shall be purchased from a reputable dealer and shall be permanently identified upon arrival. The animals shall be selected at random for the testing groups, and any animal showing signs of ill health shall not be used.

(iii) *Animal care.* (A) Animal care and housing shall be in accordance with DHEW Publication No. (NIH)-86-23, revised 1985, "Guide for the Care and Use of Laboratory Animals."

(B) The animals shall be housed in environmentally controlled rooms with at last 10 air changes per hour. The rooms shall be maintained at a temperature of 24 ± 2 degrees centigrade and humidity of 50 ± 10 percent with a 12-hour light/dark cycle per day. The animal subjects shall be kept in a quarantine facility for at least 7 days prior to use, and shall be acclimated to the experimental environment for a minimum of 48 hours prior to treatment.

(C) During the acclimatization period, the rats and guinea pigs shall be housed in suitable cages. All animals shall be provided with certified feed and tap water *ad libitum.* The guinea pig diet shall contain adequate amounts of ascorbic acid.

(2) *Administration of test substances*—(i) *Test substances.* The study will require the use of nonradioactive and radioactive test substances. These test substances shall be identical in chemical composition, and shall contain at least 40 liquid volume percent but no more than 55 liquid volume percent *n*-hexane and no less than 10 liquid volume percent methylcyclopentane (MCP) and otherwise conform to the specifications prescribed in the American Society for Testing and Materials Designation D 1836-83 (ASTM D 1836), "Standard Specification for Commercial Hexanes", published in the *1988 Annual Book of ASTM Standards: Petroleum Products and Lubricants,* ASTM D 1836-83, pp. 966-967, 1988, which is incorporated by reference. ASTM D 1836 is available for public inspection at the Office of the Federal Register, Room 8301, 1100 L Street NW., Washington, DC, and copies may be obtained from the EPA, TSCA Public Docket Office, Room NE G-004, 401 M Street SW., Washington, DC 20460. This incorporation by reference was approved by the Director of the Office of the Federal Register in

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accordance with 5 U.S.C. 552(a) and 1 CFR Part 51. This material is incorporated as it exists on the date of approval, and a notice of any change in this material will be published in the **Federal Register**. Two kinds of radioactive test substances shall be tested. ^{14}C *n*-hexane shall be the only radioactive component of one, and ^{14}C MCP shall be the only radioactive component of the other radioactive test substance.

(ii) *Dosage and treatment*—(A) *Intravenous.* The low dose of each test substance, in an appropriate vehicle, shall be administered to four rats of each sex.

(B) *Inhalation.* Two concentrations of each test substance shall be used in this portion of the study, a low concentration and a high concentration. The high concentration should ideally induce some overt toxicity, while the low concentration should correspond to the NOEL. In addition, the high concentration should not exceed the lower explosive limit of the test substance. Inhalation treatment shall be conducted using a "nose-cone" or "head only" apparatus to reduce ingestion of the test substance through "grooming."

(C) *Dermal—(1) Dermal absorption studies.* Dermal treatment should be conducted by the methodology of System, A.S., Dames, B.L. and Niemeier, R.W., "*In vivo* percutaneous absorption studies of volatile solvents in hairless mice. I. Description of a skin depot", In: *Journal of Applied Toxicology* 6:43–46, (1986), or by some other suitable modification because the test substances have significant volatility. The high and low doses shall be tested in rats and guinea pigs.

(*2*) *Washing efficacy study.* Before performing the dermal absorption studies, a washing efficacy study shall be conducted to assess the removal of the applied low dose of test substance by washing the exposed skin area with soap and water, and an appropriate organic solvent. The low dose shall be applied to separate groups of four rats and four female guinea pigs in accordance with paragraph (c)(2)(ii)(C)(*1*) of this section. Two to five minutes after application, the treated areas of two rats and two guinea pigs shall be washed with soap and water and the treated areas of the remaining animals shall be washed with an appropriate solvent. The amount of test substance recovered in the washing solutions shall be determined to assess the efficacy of its removal by washing.

(iii) *Dosing and sampling schedule*—(A) *Rat studies.* Each experimental group shall contain at least four animals of each sex. After administration of the test substance, each rat shall be placed in an individual metabolic unit for collection or urine, feces, and expired air. For the inhalation of and dermal studies, excreta from the rats shall also be colleced during the exposure periods. At the end of each collection period, the metabolic cages shall be cleaned to recover any excreta that might adhere to the cages. All studies, except the repeated dose studies, shall be terminated at 7 days, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first. All studies described below shall be conducted separately with each radiolabeled test substance.

(*1*) *Intravenous study.* Group A shall be given a single intravenous low dose of the labeled test substance (containing either ^{14}C *n*-hexane or ^{14}C MCP) at the low dose.

(*2*) *Inhalation studies.* A single 6-hour exposure period shall be used for each group.

(*i*) Group B shall be exposed to a mixture of the labeled test substance in air at the low concentration.

(*ii*) Group C shall be exposed to a mixture of the labeled test substance in air at the high concentration.

(*3*) *Dermal studies.* The test substance shall be applied and kept on the skin for a minimum of 6 hours. At the time of removal of the covering apparatus, the treated area shall be washed with an appropriate solvent to remove any test substance that may be on the skin surface. The covering apparatus components and the washing solutions shall be assayed to recover residual radioactivity. At the termination of the studies, each animal shall be sacrificed and the exposed skin area removed. An appropriate section of the skin shall be solubilized and assayed for radioactivity to ascertain whether the skin acts as a reservoir for the test substance.

(*1*) Group D shall be given one dermal, low dose of the labeled test substance.

(*ii*) Group E shall be given one dermal, high dose of the labeled test substance.

(*4*) *Repeated dosing study.* Group F shall receive a series of single daily 6-hour inhalation doses of nonradioactive test substance at the low dose over a period of at least 7 days. A single 6-hour inhalation dose of the radioactive test substance (^{14}C *n*-hexane or ^{14}C MCP) at the low dose shall be administered 24 hours after the last nonradioactive dose. Following administration of the radioactive substance, the rats shall be placed in individual metabolic cages. Excreta shall also be collected during the exposure periods. The study shall be terminated 7 days after the last dose, or after at least 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(B) *Guinea pig studies—(1) Intravenous study.* The study conducted on group A as specified in paragraph (c)(2)(iii)(A)(*1*) of this section shall be repeated using four guinea pigs per group (group G).

(*2*) *Dermal studies.* The studies conducted on groups D and E as specified in paragraph (c)(2)(iii)(A)(*3*) of this section shall be repeated using four female guinea pigs per group.

(i) Group H shall be given one dermal low dose of test labeled test substance.

(*ii*) Group I shall be given one dermal high dose of labeled test substance.

(*iii*) After administration of the test substance, each guinea pig shall be kept in a separate metabolic unit to facilitate collection of excreta. At the end of each collection period, the metabolic units shall be cleaned to recover any excreta that might adhere to them. All studies shall be terminated at 7 days, or after 90 percent of the radioactivity has been recovered in the excreta, whichever occurs first.

(3) *Types of Studies*—(i) *Pharmacokinetics studies*—(A) *Rat studies.* Groups A, B, C, D, E, and F shall be used to determine the kinetics of absorption of the test substance. In animal subjects administered the test substance intravenously (i.e., Group A), the concentration of radioactivity in blood and excreta shall be measured following administration. In animal subjects administered the test substance by the inhalation and dermal routes (i.e., Groups B, C, D, E, and F), the concentration of radioactivity in blood and excreta shall be measured at selected time intervals during the following exposure period to allow calculations of uptake, half lives, and clearance. In addition, in the groups administered the test substance by inhalation (i.e., Groups B, C, and F), the concentration of test substance in the exposure chamber air shall be measured at selected time intervals during the exposure period.

(B) *Guinea pig studies.* Groups H and I shall be used to determine the extent to which the test substance is metabolized and absorbed through the skin. The amount of radioactivity in excreta shall be determined at selected time intervals that will enable the measurement of kinetic processes.

(ii) *Metabolism studies—Rats.* Groups A, B, C, D, E, and F shall be used to determine the metabolism of the test substance. Excreta (urine, feces, and expired air) shall be collected for identification and measurement of the

quantities of test substance and metabolites.

(4) *Measurements*—(i) *Pharmacokinetics.* Four animals from each group shall be used for these purposes.

(A) *Rat studies*—(*1*) *Bioavailability.* The levels of radioactivity shall be determined in whole blood, blood plasma or blood serum at 15 minutes, 30 minutes, 1 hour, 2 hours, 8 hours, 24 hours, and 96 hours after administration of the intravenous and dermal doses, and at the same intervals after the last inhalation exposure.

(*2*) *Extent of absorption.* The total quantities of radioactivity shall be determined for excreta collected daily for 7 days, or after at least 90 percent of the radioactivity has been recovered in the excreta.

(*3*) *Excretion.* The quantities of radioactivity eliminated in the urine, feces, and expired air shall be determined separately at time intervals that provide accurate measurement of clearance and excretory rates. The collection of carbon dioxide may be discontinued when less than one percent of the dose is found to be exhaled as radioactive carbon dioxide in 24 hours.

(*4*) *Tissue distribution.* At the termination of each study, the quantities of radioactivity shall be determined in blood and in various tissues, including bone, brain, fat, gastrointestinal tract, gonads, heart, kidney, liver, lungs, muscle, skin, spleen, and residual carcass of each animal.

(*5*) *Change in pharmacokinetics.* Results of pharmacokinetics measurements (i.e., biotransformation, extent of absorption, tissue distribution, and excretion) obtained in rats receiving the single low inhalation dose of the test substance (Group B) shall be compared to the corresponding results obtained in rats receiving repeated inhalation doses of the test substance (Group F).

(B) *Guinea pig studies—Extent of absorption.* The total quantities of radioactivity in excreta shall be determined daily for 7 days or until 90 percent of the radioactive dose has been excreted.

(ii) *Metabolism.* Four animals from each group shall be used for these purposes. (A) *Rat Studies*—(*1*) *Biotransformation.* Appropriate qualitative and quantitative methods shall be used to assay urine, feces, and expired air collected from rats. Efforts shall be made to identify any metabolite which comprises 5 percent or more of the dose eliminated.

(*2*) *Changes in biotransformation.* Appropriate qualitative and quantitative assay methods shall be used to compare the composition of radioactive compounds in excreta from rats receiving single inhalation dose (Groups B and C) with rats receiving repeated inhalation doses (Group F).

(B) [Reserved]

(d) *Data and reporting.* The final test report shall include the following:

(1) *Preservation of results.* Numerical data shall be summarized in tabular form. Phamacokinetics data shall also be presented in graphical form. Qualitative observations shall also be reported.

(2) *Evaluation of results.* All data shall be evaluated by an appropriate statistical method.

(3) *Reporting results.* In addition to the reporting requirements as specified in 40 CFR Part 792, the following information shall be reported.

(i) Species and strains of laboratory animals.

(ii) Chemical characterization of the test substances, including: (A) For the radioactive test substances, information on the sites and degree of radiolabeling, including type of label, specific activity, chemical purity, and radiochemical purity.

(B) For the nonradioactive test substance, information on chemical purity.

(C) Results of chromatography.

(iii) A full description of the sensitivity, precision, and accuracy of all procedures used to obtain the data.

(iv) Percent and rate of absorption of the test substances after inhalation and dermal exposures to rats and dermal exposure to guinea pigs.

(v) Quantity and percent recovery of radioactivity in feces, urine, expired air, and blood. For dermal studies with rats and guinea pigs, include recovery data for skin, skin washings, and residual radioactivity in the recovering apparatus as well as results of the washing efficacy study.

(vi) Tissue distribution reported as quantity of radioactivity in blood, in various tissues including bone, brain, fat, gastrointestinal tract, gonads, heart, kidney, liver, lung, muscle, skin, and spleen and in residual carcass of rats.

(vii) Biotransformation pathways and quantities of the test substances and metabolites in excreta collected after administering single high and low doses to rats.

(viii) Biotransformation pathways and quantities of test substances and metabolites in excreta collected after administering repeated low doses to rats.

(ix) Pharmacokinetics models developed from the experimental data.

2. In Part 799:

a. The authority citation would continue to read as follows:

Authority: 15 U.S.C. 2603, 2611, 2625.

b. § 799.2155 by adding paragraph (c)(8) and by revising paragraph (d) to read as follows:

§ 799.2155 Commercial hexane.

* * * * *

(c) * * *

(8) *Pharmacokinetics*—(i) *Required testing.* Pharmacokinetics testing shall be conducted with the test substances specified in paragraph (a)(2) of this section and in § 795.232(c)(2)(i) of this chapter. Two separate tests will be run, one with the test substance labeled with ^{14}C *n*-hexane, and the other with the test substance labeled with ^{14}C methylcyclopentane, in accordance with § 795.232 of this chapter. In addition, the rat strain used shall be the same as the strain used in the other tests required under this section.

(ii) *Reporting requirements.* (A) The inhalation and dermal pharmacokinetics test shall be completed and the final report submitted to EPA within 18 months after [the effective date of the final rule specifying the pharmacokinetics test standard and reporting requirements for commercial hexane].

(B) Interim progress reports shall be submitted to EPA for the inhalation and dermal pharmacokinetics test at 6-months intervals, beginning 6 months after the effective date of the final test rule specifying the pharmacokinetics test standard for commercial hexane, until the final report is submitted to EPA.

(d) *Effective date.* (1) Section 799.2155 is effective on November 17, 1988 except for paragraph (c)(8) which is effective [44 days after publication of the final rule incorporating this amendment].

(2) The guidelines and other test methods cited in this section are referenced as they exist on the effective date of the respective paragraphs of this section.

[FR Doc. 88-25029 Filed 11-8-88; 8:45 am]
BILLING CODE 6560-50-M